in the parent application. The Examiner noted that references 30 to 34 were not of record in the parent application and since they had not been received, they were lined through.

Submitted herewith is a new PTO-1449 listing the references previously indicated as references 30 to 34, along with other documents as noted below, as well as the prescribed fee for submission of the same at this stage of prosecution. These references are generally review articles with respect to the development of RSV vaccines. It is regretted that these references were not submitted earlier.

The Examiner provisionally rejected claims 1 to 16 under 35 U.S.C. 101 as claiming the same invention as that of claims 1 to 16 of co-pending application 08/472,174. In the prosecution of the latter application, the applicants have elected to prosecute claims corresponding to claims 17 to 19 of this application and it is applicant's intention to delete claims 1 to 16 from application no. 08/472,174, thereby obviating any double patenting rejection.

The Examiner rejected claims 5, 7 and 8 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In this regard, the Examiner indicated that the properties of the immunogenic composition prepared by the claimed method are not clear. In view of the Examiner's comments, claim 5 has been amended to refer to the provision of non-infectious, non-immunopotentiating and immunogenic RS viral preparations, rather than the previously utilized terminology to which the Examiner raised objection. It is believed that this language now is consistent with the preparations which result from the inactivation step.

The Examiner also objected that the step of "pelleting the ultrafiltered material" is not clear in claim 12. In this regard, claim 12 has been amended to recite that the tangential flow ultrafiltration removes serum components

and provides a retentate and that it is the retentate which is pelleted by ultracentrifugation to further remove serum components. It is submitted that claim 12 is now clear in scope and consistent with the description.

Having regard to the revisions made to claims 5 and 12, it is submitted that the claims of the application are no longer open to rejection under 35 U.S.C. 112, second paragraph.

The Examiner indicated that the specification is objected to under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e., failing to provide an enabling disclosure.

In this regard, the Examiner indicated that results are not provided with respect to the BPL and ascorbic acid inactivated vaccine with respect to enhanced pulmonary pathology. In experiments that have been performed by the applicants, there has been no evidence of enhanced pulmonary pathology for the BPL and ascorbic acid inactivated vaccines. Accordingly, it is submitted that the specification is not open to objection in this respect.

The Examiner states that:

> "Protection in the cotton rat model cannot be extrapolated to humans. Due to the unpredictability of RSV vaccines to provide protection in humans, it would require undue experimentation to determine how to use the claimed vaccine compositions to provide protection in humans."

It is submitted that this rejection is nothing more than an objection of lack of utility. Indeed, in the parent application, the Examiner had rejected the claims under 35 U.S.C. 101 as lacking patentable utility and stated:

> "Because of the shortcomings of the cotton rat animal model as an animal model for RSV as discussed above, it is not possible to extrapolate the effectiveness of the vaccine from results of the cotton rat model to the effectiveness of the vaccine in humans."

It is clear from this quotation that the Examiner is using precisely the same justification for a rejection of the claims under 35 U.S.C. 101 as lacking utility in the parent application and an objection to the specification under 35 U.S.C. 112, first paragraph, in this application referring instead to "undue experimentation". It is submitted that the PTO Examination Guidelines on Utility Requirement do not permit the Examiner to raise the objection that is raised in the absence of a rejection under 35 U.S.C. 101. In any event, it is submitted that the specification clearly discloses a utility for the claimed compositions, namely as a vaccine to protection from RSV infection in humans without causing enhanced pulmonary pathology.

The applicants are mindful that 35 U.S.C. 112, first paragraph, addresses matters other than those related to the question of whether or not an invention lacks utility. However, the Examiner cannot utilize an objection to the specification under 35 U.S.C. 112, first paragraph, as a disguised rejection of lack of utility. The Examiner's utilization of precisely the same basis and almost precisely the same language, to support a rejection of the claims under 35 U.S.C. 101 in the parent application and an objection to the specification under 35 U.S.C. 112, first paragraph, in this application, clearly indicates that this is precisely what the Examiner is doing. On this basis alone, the objection to the specification under 35 U.S.C. 112, first paragraph, and the rejection of claims 1 to 4, 15 and 16 under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification, should be withdrawn.

In any event, it is submitted that it would not require "undue experimentation" to determine how to use the claimed vaccine composition to provide protection in humans. The manner of determining effective doses, mode and frequency of administration are well within the routine skill of the art

to determine. There is no undue experimentation which is involved.

The applicants have clearly shown protection in the accepted animal model of the RSV infection, namely the cotton rat. Whether or not the effectiveness of the vaccine based on results achieved in the cotton rat model may not necessarily be extrapolated to humans is immaterial, if the cotton rat model is an accepted animal model of the infection.

In any event, there is a direct correlation between antibody titres in the sera of cotton rats which inhibit significant pulmonary resistance to RSV infection and infants younger than two months of age who exhibit relative resistance to serious RSV respiratory tract disease. These resistant infants have passively acquired RSV serum neutralizing antibodies of the same mean titres (1:200 to 1:300) as cotton rats, as described by the Chanock reference, to which the Examiner refers. It is clear, therefore, that an immunogen which produces an appropriate titre of neutralizing antibodies in cotton rats provides a prediction of protection in humans by that immunogen. The Examiner appears to have conceded that applicant's data shows the generation of neutralizing antibodies in cotton rats.

The Examiner refers to articles by McIntosh et al and Collins et al in support of her position. However, the Examiner's attention is also directed to Murphy et al, WO 93/21310 which states:

> "... the cotton rat appears to be a reliable experimental surrogate for the response of infected monkeys and humans to immunotherapy with RSV neutralizing antibodies. For example, the amount of RSV neutralizing antibodies associated which a therapeutic effect in cotton rats as measured by the level of such antibodies in the serum of treated animals (i.e., serum RSV neutralizing titre of 1:320 to 1:518) is in the same range as that demonstrated for monkeys (i.e., 1:877). A therapeutic effect in cotton rats was manifested by a one hundred fold or greater reduction in virus titer in the lung (Price et al, J. Virol., 61:1851-1854) while in monkeys a

> therapeutic effect was observed to be a 50-fold reduction in pulmonary virus titre (Hemming et al, J. Infect. Dis., 152:1083-1087 (1985)."

Murphy et al conclude:

> "Based on these studies, it would appear that the cotton rat constitutes a relevant model for predicting the success of an RSV vaccine in infants and small children."

Accordingly, despite the comments of the Examiner, those skilled in the art consider the cotton rat to be the relevant model for predicting the success of an RSV vaccine is useful in infants and small children. Accordingly, applicant's data, as presented in the application, can be extrapolated to humans.

Further, Prince et al (J. Virol. 55; 517; Virus Res. 3; 193) found that administration of RSV-specific neutralizing antibodies could not only prevent RSV infection in the lungs of infant cotton rats when administered prior to virus exposure, but also rapidly resolved infection when given at the height of infection. Crowe et al. (PNAS 91; 1386) has stated that:

> "Clinical trials have validated these aforementioned experimental observations." (col. 2, page 1386).

Groothuis et al (N. Engl. J. Med. 329:1524) have reported that:

> "Administration of high doses of RSV immune globulin is a safe and effective means of preventing lower respiratory tract infection in infants and young children at high risk for this disease." (see col. 2; abstract).

Accordingly, the results obtained in cotton rats were supported by data obtained in human trials.

Results from a recent clinical trial which evaluated the safety and immunogenicity of an RSV subunit vaccine provides additional evidence that the data obtained in cotton rats has clinical relevance. An immunoaffinity-purified F protein preparation was highly immunogenic and protected

cotton rats against live virus challenge (Walsh et al, J. Infec. Dis., 155; 1198). This subunit preparation was also proved to be safe and immunogenic in seropositive toddlers (Paradiso et al., Pediatr. Infect. Dis. J. 13; 792). (A copy of each of the references referred to above is enclosed and also listed on the enclosed PTO-1449.

Based upon this data, it is clear that the results obtained in cotton rats have clinical relevance. Accordingly, even if the Examiner's objection to the specification was properly made, there is no basis for asserting that it would require undue experimentation to determine how to use the claimed vaccine compositions to provide protection in humans.

With respect to the Collins et al reference to which the Examiner referred, one must take into consideration several alternative explanations as to why the vaccinia-RSV recombinants used by Collins et al induced a protective immune response in cotton rats and owl monkeys and yet had poor efficacy in chimpanzees. While, as the Examiner points out, Collins et al suggests that due to the permissiveness of the chimpanzee for RSV replication, it may be more difficult to protect immunized animals against live virus challenge. However, one must not ignore the alternative reasons proposed by Collins et al to explain the immunoprotective ability of the vaccinia-recombinants in cotton rats and the apparent lack of efficacy of the recombinants in chimpanzees. As stated by Collins et al:

> "The greater immunogenicity of the vaccinia-RSV recombinants in cotton rats (and mice) probably is due in large part to the propensity of vaccinia virus to initiate systemic infections in rodents, in contrast to the localized dermal infections observed in primates. Dissemination by vaccinia virus resulting in extensive infection at secondary sites such as the liver was directly observed in cotton rats in a separate experiment that involved subcutaneous innoculation. This more generalized infection would result in a greater quantity and wider distribution of RSV-F and G glycoprotein

> expression, which would result in a heightened immune response". (page 167, col. 1).

Collins et al concluded that:

> "It remains to be determined whether this vaccine failure is specific to the chimpanzee, to the use of a recombinant vaccinia virus, to insufficient antigen, or to the parenteral route of immunization." (page 167, col. 2).

Accordingly, it is premature to conclude that the vaccinia-RSV recombinants would be non-efficacious in humans. Indeed, the cotton rat data obtained with the vaccinia-RSV recombinants may have clinical relevance.

It should further be noted that both chimpanzees in the second group which were immunized with the vaccinia F and G recombinants developed a relatively high level of RSV-specific neutralizing antibodies and exhibited significant pulmonary protection. Thus, the recombinants were able to elicit a protective immune response in some chimpanzees. In this case, the results were more comparable to the data obtained with cotton rats. An additional important point is that the chimpanzee model has its own drawbacks. According to Crowe et al, (Vaccine 11, 1396):

> "Juvenile chimpanzees of the age used in this study (evaluation of the vaccinia-RSV and live attenuated viruses) do not exhibit clinical signs of lower respiratory tract disease, even in the face of documented wild-type virus replication in that site. Thus, attenuation of disease in the lower respiratory tract would not be studied directly in such primates under the experimental conditions of our study". (page 1402, col. 1).

Accordingly, one can only postulate that the results observed in the primates will also occur in humans.

Accordingly, it is submitted that the objection to the specification under 35 U.S.C. 112, first paragraph, and the rejection of claims 1 to 4 and 15 to 16 under 35 U.S.C. 112, first paragraph, for reasons set forth in the objection to the specification should be withdrawn.

The Examiner also objected to the specification under 35 U.S.C. 112, first paragraph, with respect to enhanced pulmonary pathology with respect to the BPL and ascorbic acid inactivated vaccines. As already noted above, in applicant's experiments, no evidence of enhanced pulmonary pathology with either the BPL inactivated vaccine or the ascorbic acid activated vaccine exists. The Examiner appears to concede that applicant's specification clearly provides evidence that the OG-inactivated RS virus preparation elicited a protective immune response without causing enhanced pulmonary pathology.

It is further noted that formalin-inactivated RSV compositions consisted on a crude preparation of RSV inactivated with a high concentration of formaldehyde and further adjuvanted with a high amount of aluminum phosphate. The high concentration of formaldehyde in that preparation made in the 1960's almost certainly would result in a change in the conformation of the F and probably the G protein of RSV. In contrast, the applicants prepared the inactivated RS virus under non-denaturing conditions and inactivation under conditions acceptable for use in human vaccines. There is no comparison between the two formulations and the Examiner cannot rely on the results of a formalin-inactivated material for any prediction or lack of prediction of the effect of the materials which are used in the present invention, having regard to the significantly different process conditions employed.

Accordingly, it is submitted that the specification is not open to objection under 35 U.S.C. 112, first paragraph, on this ground and that the rejection of claims 1 to 7, 9, and 10 to 16 under 35 U.S.C. 112, first paragraph, for the reasons of objection to the specification, should be withdrawn.

The Examiner rejected claim 1 under 35 U.S.C. 102(e) as being anticipated by Bordt et al.

Claim 1 defines an immunogenic composition capable of producing a respiratory syncytial virus specific immune

response in a host immunized therewith. The composition comprises a purified, inactivated RS viral preparation which is substantially free from cellular and serum components and which is non-infectious, non-immunopotentiating, immunogenic and protective, together with a carrier therefor. While it is true that the Bordt et al reference discloses a bovine respiratory syncytial virus inactivated with ascorbic acid, as stated by the Examiner, nevertheless, it is also clear from the description in Bordt et al that the vaccine composition is in no way purified. While the Examiner indicates that Bordt et al is silent as to whether the virus is substantially free from cellular and serum components, and asserts that the product of Bordt et al "appears to be in a purified state", it is submitted that such is not the case. It is clear from Example I that the ascorbic acid is added to virus fluid to effect the inactivation and this viral fluid is not further processed in any way which would result in purification of the material. Accordingly, it is submitted that claim 1 is not open to rejection under 35 U.S.C. 102(e) as being anticipated by Bordt et al.

The Examiner rejected claims 2 to 4, 15 and 16 under 35 U.S.C. 103 as being unpatentable over Bordt et al in view of McIntosh et al. The Bordt et al reference has been discussed above. The McIntosh et al reference would not appear to add anything to Bordt et al in terms of the provision of a purified inactivated RS viral preparation substantially free from cellular and serum components, as required by applicant's claims. As the Examiner states, McIntosh et al teach that human RSV is the most important cause of viral lower respiratory tract disease in infants and children and that human RSV is a paramyxovirus. While it is true that Bordt et al teach that paramyxoviruses may be inactivated by ascorbic acid and that RSV is a paramyxovirus, as taught by McIntosh, neither reference discloses or suggests

the provision of a purified RS viral preparation, as required in the present invention.

Accordingly, it is submitted that claims 2 to 4, 15 and 16 are not open to rejection under 35 U.S.C. 103 as being unpatentable over Bordt et al in view of McIntosh et al and hence, the rejection should be withdrawn.

The Examiner rejected claims 5 and 6 under 35 U.S.C. 103 as being unpatentable over Downing et al in view of Preston et al.

As is set forth in the introductory portion of the specification, for many years the production of an RS virus vaccine has been hampered by the adverse effects produced with a formalin-inactivated RS virus vaccine in a human clinical trial done in the United States in the 1960's. In the last 30 years, the efforts of the vaccine producers have concentrated on the production of live attenuated RS virus mutants or subunit vaccines, rather than the use of inactivating agents for the generation of an RS virus vaccine. In this regard, the Examiner's attention is directed to the various review articles which are listed on the enclosed PTO-1449 which quite clearly show that no consideration is being given by the art to the inactivation of virus for providing an RS virus vaccine. To date, no vaccine manufacturer or research laboratory has envisioned or suggested the use of inactivating agents for the production of a human RS virus vaccine. While it is true that the Downing et al reference teaches a method of preparing respiratory syncytial virus by growing the RSV on HEp-2 cells, the specific aim of this study was:

> "To determine if the viral matrix cellufine sulfate (MCS) interaction is indeed electrostatic and if the intact virus was required for binding and to determine an optimal elution scheme that maximized the separation of virus from cellular proteins and maximized the yield and concentration in the viral fractions".

The aim of the present application is purify virus to remove contaminating cellular and serum proteins to avoid the

potential problem of non-viral proteins which enhance pulmonary pathology following exposure to wild-type virus. The objectives of the paper and the present application, therefore, are distinctly different.

As the Examiner correctly points out, the Downing et al reference does not teach inactivating the virus with β-propiolactone or indeed, any other inactivating agent. Indeed, as noted above, there is prejudice in the art against inactivating RS virus for the purposes of providing vaccine compositions in view of the problems associated with such inactivation using formalin.

The purpose of the Preston study was to understand the immune response relating to the reduced resistance to subsequent RSV infections by in vitro studies aimed at inhibiting the proliferative T-cell response to inactivated RSV. The purpose of the β-propiolactone used in this study was to prepare inactivated RSV to be used only to stimulate the adult mononuclear cells for the purpose described above. The Preston et al reference contains no suggestion for inactivating virus which has been processed in accordance with applicant's recited process steps and indeed, there is no motivation whatsoever in either Downing et al or Preston et al to use the β-propiolactone inactivation described in Preston on the materials which are prepared by Downing. Indeed, as noted above, the art points away from any such activity.

Accordingly, it is submitted that claims 5 and 6 are patentable over the combination of Downing et al in view of Preston et al and accordingly, the rejection of claims 5 and 6 under 35 U.S.C. 103 as being unpatentable over this combination of art, should be withdrawn.

The Examiner rejected claims 5 and 9 under 35 U.S.C. 103 as being unpatentable over Downing et al in view of White et al. The teachings of Downing et al and the deficiencies thereof have already been discussed above. As the Examiner notes, Downing et al do not teach inactivating the virus with

ascorbic acid. In addition, there is no suggestion whatsoever in Downing to effect any such inactivation.

The White et al reference apparently is relied on for a teaching of inactivation of RSV by a treatment with ascorbic acid. The objective of the study reported by White et al was to determine the in vitro effect of ascorbic acid on viruses and to use the inactivated virus as a reagent in serologic assays, and not for the production of an inactivated RSV vaccine. As described in White et al, the infected cells are grown in roller bottles, scraped, disrupted by a freeze-thaw cycle and further clarified by centrifugation. This means of virus purification would not yield a viral preparation free of cellular contaminants. In addition, there would be no reason for a person skilled in the art to apply the teaching of White et al with respect to inactivation using ascorbic acid to the teachings of Downing et al in view of the clear prejudice in the art against inactivated preparations.

Accordingly, it is submitted that claims 5 and 9 are patentable over the combination of Downing et al in view of White et al and accordingly, the rejection of claims 5 and 9 under 35 U.S.C. 103 as being unpatentable over this combination of prior art should be withdrawn.

The Examiner rejected claims 5, 7 and 8 under 35 U.S.C. 103 as being unpatentable over Downing et al in view of Prince and Georgiades et al.

The Downing et al reference and its deficiencies have been discussed in detail above.

The Prince et al reference is apparently cited for a teaching of inactivation of plasma hepatitis virus by treatment with a non-ionic detergent which may be n-octyl-β-D-glycopyranoside. The Georgiades et al reference apparently is relied on for a teaching of inactivation of contaminating viruses in interferon α solutions by treatment with non-ionic detergents.

The Prince et al reference relates to the use of non-ionic detergents to sterilize blood plasma so that it is free of active hepatitis virus. There are distinct differences between the hepatitis virus and RSV. Hepatitis B is a DNA virus belonging to the hepadnaviridae family of viruses, while RSV is a negative strand RNA virus belonging to the paramyxoviridae virus family. The conditions found suitable for inactivating viruses belonging to the hepadnaviridae family of viruses may not be suitable for viruses belonging to the paramyxoviridae family. In the Prince et al reference, it is recommended that a combination of a non-ionic detergent, alcohol or ether or a mixture of both be used to inactivate hepatitis viruses during plasma processing. Detergent alone is used in the present application to inactivate RSV.

The Georgiades et al reference deals with the process for the purification of interferon α and to a method of enhancing the overall recovery of interferon α. The purpose of using the detergent in the reference was to eliminate virus contamination and not to produce killed viral vaccines.

As previously noted, the art is prejudiced against using inactivated RS virus for vaccine use and there is no motivation in the cited prior art to inactivate RS virus using non-ionic detergents, in particular, glucopyranosides. Accordingly, it is submitted that claims 5, 7 and 8 are patentable over the combination of Downing et al in view of Prince and Georgiades et al and hence, the rejection of those claims under 35 U.S.C. 103 as unpatentable over this combination of prior art should be withdrawn.

The Examiner rejected claims 5, 10, 12 and 13 under 35 U.S.C. 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al.

The Ewasyshyn et al reference describes the production of purified surface glycoproteins of RSV and PIV-3.

The only similarity or relevance to the present invention is that both the present invention and Ewasyshyn et al describe growing and harvesting RS virus. Thereafter, the processes diverge significantly. The present invention further processes the harvested whole virus, while Ewasyshyn et al then solubilize and isolate glycoproteins from the harvested virus. The Ewasyshyn et al reference does not teach inactivation of virus, as noted by the Examiner. This is because the Ewasyshyn et al procedure extracts the surface glycoproteins from the virus and is concerned solely with processing that extracted material.

The Examiner indicates that the Mbiguino et al reference is relied on for a teaching of purification of RSV under non-denaturing conditions using a sucrose gradient. The protocol described by Mbiguino et al is cumbersome and time-consuming and in any event, unrelated to vaccine development. The rationale employed by Mbiguino et al for producing a highly purified preparation of RSV was not to eliminate contaminating cellular and serum proteins which may contribute to enhanced pulmonary pathology following live virus challenge, but rather was to compare different gradients, namely sucrose, percol, renografin and metrizamide, for purifying RSV.

It is clear, therefore, that claims 5, 10, 12 and 13 are patentable over this combination of prior art since whatever modification the Examiner proposes to make to the Ewasyshyn et al procedure, that procedure is concerned with producing different materials from the product of the present invention and hence, the combination of prior art is irrelevant to the claimed invention.

Accordingly, it is submitted that claims 5, 10, 12 and 13 are not open to rejection under 35 U.S.C. 103 as being unpatentable over the combination of Ewasyshyn et al and Mbiguino et al and hence, the rejection should be withdrawn.

The Examiner rejected claim 11 under 35 U.S.C. 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al as applied to claims 5, 10, 12 and 13 and further in view of McIntosh et al and Paradiso et al.

The deficiencies of the teachings of Ewasyshyn et al and Mbiguino et al have been discussed above and do not require further discussion. Claim 11 is concerned specifically with growing the RS virus on VERO cells and as the Examiner points out, McIntosh and Paradiso both describe the use of VERO cells for growing RS virus. The McIntosh et al and Paradiso et al references would not appear to remedy the defects of the basic combination of Ewasyshyn et al and Mbiguino et al as discussed above.

Having regard to those defects, it is submitted that claim 11 is not open to rejection under 35 U.S.C. 103 as being unpatentable over the combination of Ewasyshyn et al, Mbiguino et al, McIntosh et al and Paradiso et al and hence, the rejection should be withdrawn.

The Examiner rejected claim 14 under 35 U.S.C. 103 as being unpatentable over Ewasyshyn et al in view of Downing et al and Kuchler. The disclosures of the Ewasyshyn et al and Downing et al references have previously been discussed. The Kuchler reference apparently is relied on for a general teaching of the steps involved in purification of viruses generally describing the use of the chromatographic and ion-exchange resins, molecular sieving on gel filtration columns, countercurrent distribution or by gradient centrifugation. This reference, therefore, is nothing but a general teaching of common purification operations. Claim 14 defines a specific combination of purification steps which, it is submitted, is nowhere disclosed or suggested in the Kuchler reference.

Having regard to the deficiencies of the Ewasyshyn et al and Downing et al references as outlined above, and having regard to the lack of specificity in the Kuchler

reference with respect to the process steps employed in claim 14, it is submitted that claim 14 is clearly patentably distinguished from the prior art that the Examiner relies on. Accordingly, it is submitted that the rejection of claim 14 under 35 U.S.C. 103 as being unpatentable over Ewasyshyn et al in view of Downing et al and Kuchler, should be withdrawn.

It is believed that this application now is in condition for allowance and early and favourable consideration and allowance are respectfully solicited.

Respectfully submitted,

M. I. Stewart

Michael I. Stewart
Reg. No. 24,973

Toronto, Ontario, Canada
(416) 595-1155
FAX No. (416) 595-1163